REMARKS

Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 are pending in the present application.

The rejections of: (a) Claims 11, 14-23, 26-30, 33-34, and 39-49 under 35 U.S.C. §103(a) over Cutie (U.S. 5,891,419) in view of Tzou et al. (U.S. 5,776,433); (b) Claims 35-38 under 35 U.S.C. §103(a) over Cutie (U.S. 5,891,419) in view of Tzou et al. (U.S. 5,776,433) and Riebe et al (U.S. 6,558,651); and (c) Claims 12-15, 20, 24-25, 27, and 31-32 under 35 U.S.C. §103(a) over Cutie (U.S. 5,891,419) in view of Tzou et al. (U.S. 5,776,433) and Radhakrishnan et al (U.S. 5,192,528), are obviated in part by amendment and traversed in part.

Cutie discloses aerosol formulations for oral inhalation containing flunisolide ***dispersed*** in HFC 134a and/or HFC 227 (see Abstract). The aerosol formulations disclosed by Cutie are free of CFCs and surfactants, and contain little or no ethanol. In regard to the small amounts of ethanol, Cutie discloses at column 4, lines 5-16 that ethanol is present to ***prevent dissolution*** of the flunisolide. However, this disclosure is directly at odds with the present invention wherein a cosolvent (e.g. ethanol) is used to *dissolve* the active ingredient in the propellant (see, for example, pages 10-12 and the Examples). From this disclosure by Cutie, it is clear that ethanol is not a cosolvent as used in the present invention as its function in the aerosol formulation is substantially different from that of a cosolvent, which is presently claimed.

First, it should be noted that Cutie makes no disclosure as to budesonide. Therefore, this reference, even when combined with Tzou et al, Riebe et al, and/or Radhakrishnan et al, is not relevant toward the claims of the present application in which the corticosteroid is not

defined as budesonide. As such, Applicants submit that the presently claimed invention would not be obvious.

Applicants submit the following additional reasons why the presently claimed invention is not obvious in view of Cutie when combined with Tzou et al, Riebe et al, and/or Radhakrishnan et al.

In the presently claimed invention, budesonide is required to be ***completely dissolved*** in the propellant vehicle (see Claims 11, 19, and 26). Therefore, Applicants submit that the disclosure of Cutie falls far short of disclosing or suggesting the claimed invention.

Further, Cutie widely expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be inhaled and contributing to particle size growth" (column 1, lines 60-65). As such, Cutie favors avoiding that which the present invention claims.

Applicants again note that MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In view of the disclosure at column 4, lines 5-16, Applicants note that Cutie teaches away from the inclusion of ethanol as a cosolvent and/or the complete dissolution of the corticosteroid in the propellant vehicle. Therefore, the disclosure by Cutie fails to render the present invention obvious.

Additionally, in spite of the general disclosure that the drug may be dissolved in the propellant, all the specific teaching of Cutie is directed to suspension formulations that, as also pointed out by the examiner, *require a sugar* as a necessary component of

the formulation acting as a dispersant. More specifically Cutie discloses flunisolide aerosol formulations wherein flunisolide is dispersed in the propellant (column 3, fine 35) and wherein the cosolvent (ethanol) merely aids in dispersing the drug (column 4, line 5). The formulations may contain ethanol, but when ethanol is present it comprises less than 5% of the formulation (column 5, lines 5 and 6). On the contrary, Example 3 of the present invention shows that at least 13% w/w ethanol is necessary to solubilize 12 mg of budesonide in the formulation. Therefore, Cutie fails to achieve yet another limitation of the claimed invention – complete dissolution of budesonide. Furthermore, Cutie lacks disclosure on canister specifics and does not account for the chemical stability of the active ingredient.

Tzou describes aerosol compositions comprising flunisolide, ethanol and HFA propellants and outlines that certain excipients, e.g. certain surfactants, flavoring agents, and/or water are beneficial to some embodiments of the invention. Again, no reference is made in this disclosure of budesonide.

In particular the chemical stability of certain formulations of flunisolide is enhanced by the presence of *water, sorbitan trioleate and cetylpyridinium chloride* (page 5, lines 1-30). It is also stated that conventional aerosol canisters can be used for keeping the composition and that certain containers enhance the chemical stability of certain formulations and/or minimize the *absorption* of flunisolide onto the container walls. It is suggested that the composition be *preferably kept within a glass aerosol vial* or an aluminium aerosol vial having an interior formulation chamber coated with a resin that is inert to flunisolide and preferably does not *absorb* flunisolide from the formulation, like epoxy resins (e.g. epoxy phenol resins and epoxy urea formaldehyde resins; page 7, lines 3-17).

Tzou also discloses that flunisolide has been previously provided in the form of a nasal formulation in a solution of propylene, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride and purified water.

In the outstanding Office Action, the Examiner alleges that it would have been obvious to the skilled artisan at the time the invention was made given the general formulations of Cutie to have looked in the art for specific antioxidants and specific aerosol canisters that would improve stability and efficiency of the inhaled formulations as taught by Tzou. Applicants respectfully disagree.

First, all the skilled artisan would learn from Cutie is that a sugar and especially micronized beta lactose is necessary in the formulation for aiding in the incorporation, dispersion and solubilization of drugs and excipients in the propellant (col 3, lines 12 -- 18). Moreover, from the teaching of Tzou the skilled artisan will come to the conclusions that the presence of water and sorbitan trioleate as well as cetylpyridinium chloride in a suitable concentration enhances the chemical stability of certain flunisolide HFA formulations and that there is no difference regarding the properties of glass containers and containers coated with epoxy phenol resin and, given the presence of water and/or of some special additives, aluminium containers.

On the other hand, in spite of all the general information on enhanced chemical and physical stability of flunisolide in solution in a hydrofluorocarbon propellant and ethanol, Tzou does not provide any teaching on how the problem of chemical stability of budesonide in hydrofluorocarbon and ethanol solutions can be solved. Moreover, Tzou does not suggest in any way to add to an HFA propellant based flunisolide formulation an antioxidant. Therefore, there would be no motivation for the skilled in the art to add an antioxidant to an HFA

solution formulation of budesonide on the sole basis of generic information concerning an aqueous solution of flunisolide comprising butylated hydroxyanisole among several excipients of various kinds.

Riebe et al disclose the use of a recrystallised form of salbutamol sulphate to reduce or eliminate the problem of drug *adhesion or deposition* to the inner surfaces of the MDI. The use of an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated can help to reduce even further *the deposition or adhesion* of salbutamol sulphate on the inner surfaces of the can.

It is important to note that Riebe et al deals with the specific problem of the adhesion of *particulate salbutamol* to the walls of the can. There would be no reason for the skilled in the art to turn to Riebe et al to solve the problem of the *chemical degradation* of budesonide in solution in an HFA propellant, as this reference makes no reference of budesonide, much as in the case of Cutie and Tzuo et al.

Moeover, Applicants submit that there is even less motivation for the skilled in the art to combine the disclosure of Riebe et al with Tzou et al, since Tzou et al disclose the use of water and sorbitan trioleate as well as cetylpyridinium chloride in suitable concentrations to enhances the chemical stability of certain flunisolide HFA formulations.

The Examiner cites Radhakrishnan et al as disclosing corticosteroid inhalation treatment methods of delivering said corticosteroid drug to the lungs. The corticosteroids include flunisolide, budesonide, etc. The examiner observes that the formulation described in example 1 is formed by adding alpha-tocopherol with the corticosteroid and lipids and (editor's note) further excipients (col. 4, lines 34-37). However, Radhakrishnan et al. fails to compensate for the deficiency note above for Cutie.

Applicants note that the formulation disclosed by Radhakrishnan et al. is in the form of an *aqueous liposome suspension.* Such a formulation is physically distinct from the formulation of the present invention, as well as Cutie, which is an aerosol formulation. As such, there would be no motivation to combine the disclosures of Cutie and Radhakrishnan et al.

Applicants note that the mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness (MPEP §2143.01). Applicants remind the Examiner that "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." (*In re Fritch* 23 USPQ2d 1780, 1783 (Fed. Cir. (1992)). In view of the differences noted above in the type of formulation disclosed in Cutie (aerosol) and Radhakrishnan et al. (aqueous liposome suspension), Applicants note that absent a specific suggestion or incentive in the references themselves their would be no motivation to combine the disclosures of Cutie and Radhakrishnan et al. As such, the present invention is not obvious in view of the disclosures of Cutie and Radhakrishnan et al.

Applicants further submit that Radhakrishnan et al teaches away from the use of a formulation in the form of a drug-solute propellant solvent system that, in their opinion, offer poor control of particle size, can provoke irritation effects for the presence of the solvent and is unsuitable for delivery to the deep lung (cfr col. 9, lines 14-17 and lines 23-26). The Examiner is again directed to MPEP §2141.02 states and is reminded that portions of a reference that lead away from the claimed invention must be considered.

The presently claimed invention is directed to HFA propellant based budesonide solution formulations wherein the active ingredient is ***completely dissolved*** in the propellant vehicle and is chemically stable. Simply, none of the cited prior art or combined disclosures of the cited prior art disclose or suggest how the problem of chemical stability of budesonide in hydrofluorocarbon and ethanol solutions can be solved.

In view of the foregoing, withdrawal of this ground of rejection is requested.

The rejection of Claims 11, 14-19, 21-23, 26, and 28-30 under 35 U.S.C. §103(a) over Rovee et al (U.S. 4,185,100) in view of Cutie (U.S. 5,891,419) is obviated in part by amendment and traversed in part.

Rovee et al. relates to a pharmaceutical composition for topical treatment of skin disorders. The topical vehicle may be a cream, lotion, gel or other form acceptable for topical use. Substantially, the disclosure of Rovee et al. relates to compositions that are a liquid preparation for topical administration and contain one or more solvents, including ethanol and propylene glycol (see, for example, column 3, lines 25-26, Table A, and Table B). However, preparations for topical administration do not contain propellants.

In regard to the propellants, the Examiner points to the Table under sub-heading "F. Aerosol" appearing in column 7. In sub-heading "F. Aerosol" Rovee et al. disclose that aerosol formulations can be obtained in accordance with their invention. To this end, Rovee et al. state that a propellant may be used. However, the only propellant disclosed therein is the propellant appearing in the Table that provides the composition for a quick breaking alcoholic foam. The vehicles can vary with the type of the propellant and of the concentrate, which can contain from about 8.5 to 50.0% of water. A preservative can be added, but antioxidants are not mentioned at all.

Moreover, Rovee et al. provides compositions of triamcinolone acetonide in a solvent system constituted of propylene glycol/ethanol 50/50 by volume, but does note specifically disclose or suggest triamcinolone acetonide with a propellant or specifically disclose or suggest HFA propellants at all.

The examiner recognizes that Rovee et al lacks specific disclosure on HFA propellants, but on the other hand deems that it would have been obvious to the skilled artisan at the time the invention was made given the general formulations of Rovee et al to have looked in the art for suitable propellants as taught by Cutie, with a reasonable expectations of successfully preparing safe and effective aerosol preparations. Applicants respectfully disagree and submit that the present invention would not be obvious in view of the combined disclosures of Rovee et al. and Cutie.

In Rovee et al. antioxidants are only disclosed in column 4, lines 41-44 and column 5, lines 45-49 in connection with the preparation of a topical cream of oil in water emulsion type and aqueous/alcoholic solutions, respectively. Moreover, Rovee et al. is *completely silent about budesonide* and only provides compositions of triamcinolone acetonide in a solvent system constituted of propylene glycol/ethanol 50/50 by volume. Rovee et al does not specifically disclose or suggest triamcinolone acetonide with a propellant or specifically disclose or suggest HFA propellants at all.

Cutie discloses flunisolide aerosol formulations wherein flunisolide is ***dispersed*** in the propellant (column 3, line 35) and wherein the cosolvent (ethanol) merely aids in ***dispersing*** the drug (column 4, line 5). Cutie widely expounds the difficulties inherent in the preparation of aerosol formulations with HFA propellants (column 1, lines 44-60) and discourages the use of a co-solvent in solution formulations, to enhance drug dissolution, in that "this practice may have the disadvantage of decreasing the fraction of the metered dose which may be

inhaled and contributing to particle size growth" (column 1, lines 60-65). However, in the presently claimed invention, budesonide is required to be ***completely dissolved*** in the propellant vehicle (see Claims 11, 19, and 26). This is neither disclosed nor suggested by the combined disclosures of Rovee et al. and Cutie.

Further, it should be noted that, as in the case of Rovee et al., Cutie. is also *completely silent with respect to budesonide* and only provides compositions of flunisolide. Therefore, since neither Rovee et al nor Cutie disclose or suggest a formulation containing budesonide, these combined references cannot render the present invention obvious.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 11 and 15-23 under 35 U.S.C. §103(a) over Keller et al. (WO98/34595) is obviated in part by amendment and traversed in part.

Keller et al. disclose a pressure-liquified propellant mixture for aerosols, where the propellant mixture is ***based on carbon dioxide*** (see column 5, lines 23-25) contains as ***required*** ingredients a fluorinated alkane (e.g., 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane) ***and*** carbon dioxide (see, for example, Abstract, page 5, lines 23-25, and the claims). Such a disclosure is distinct from the aerosol formulation as presently claimed in which the propellant vehicle used to dissolve budesonide ***only*** consists of one or more hydrofluoroalkanes and a cosolvent. Accordingly, the propellant vehicle of the present invention ***excludes*** carbon dioxide, which is a required component in the propellant mixture of Keller et al. As such, Applicants submit that Keller et al. does not render obvious the presently claimed invention.

The Examiner alleges that the foregoing argument is not "commensurate with the claims. Instant claims are formulation claims which us the open language of "comprising"

Use of CO2 in the instant formulations is not excluded." Applicants do not disagree that carbon dioxide may be in the final formulation by virtue of the term "comprising." However, the question in the present application is whether carbon dioxide is excluded at some other critical step, which is the case here. The plain language of the claimed aerosol formulation, metered inhaler, and method require that the propellant vehicle used to dissolve budesonide ***only*** consists of one or more hydrofluoroalkanes and a cosolvent as is clearly manifest in the use of the term "consisting of." Accordingly, the propellant vehicle of the present invention ***excludes*** carbon dioxide during dissolution of budesonide.

Again, the Examiner is reminded that MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Therefore, the explicit disclosure by Keller et al that it is required that a carbon dioxide be present in the propellant mixture directly teaches away from the claimed invention. As such, Keller cannot affect the patentability of the claimed invention.

Further, with respect to the disclosure of Keller et al., Applicants note that this disclosure points out the various disadvantages associated with the use of the HFA propellants, in particular with respect to the preparation of suspension formulations (see from column 2, line 61 to column 3, line 52). One important disadvantage of the HFAs is their low dissolving power in comparison to the old CFC propellants (column 3, lines 7-9), which can be increased by addition of polar solvents, such as, for example, ethanol. However, Keller et al. caution that in ethanol-containing solution aerosols problems often occur relating to the active compound stability (column 4, lines 62-64).

Keller et al. solve the foregoing "problems" by using a propellant mixture based on carbon dioxide (column 5, lines 23-25) allowing for improvements of the characteristics of both suspension and solution aerosols. At column 10, lines 32-34, Keller et al. declares in general terms that the aerosol formulations can further contain buffer substances or stabilizers such as vitamin E, without making specific reference to solutions or suspensions. However, Keller et al specifically disclose the indispensable use of carbon dioxide to prepare solution aerosols having improved storage stability.

The present invention offers a specific solution to the preparation of budesonide solution formulations in an HFA propellant. Specifically, the present invention provides a solution by adding an antioxidant to the propellant vehicle where the propellant vehicle only consists of one or more hydrofluoroalkanes and a cosolvent (i.e., excludes carbon dioxide).

In view of the foregoing, Applicants submit that the present invention is not obvious in view of the disclosure of Keller et al. Therefore, withdrawal of this ground of rejection is requested.

Applicants respectfully request that the provisional obviousness-type double patenting rejection of Claims 11-32 over the claims 1-13 of U.S. 10/244,519 be held in abeyance until an indication of allowable subject matter in the present application. If necessary, a terminal disclaimer may be filed at that time. Until such a time, Applicants make no statement with respect to the propriety of this ground of rejection.

Applicants respectfully submit that the above-identified application is now in condition for allowance, and early notice of such action is earnestly solicited.

Respectfully submitted,

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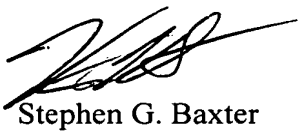

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